II. REMARKS:

A. Status of the Claims

Claims 1-22 were originally filed with the case. Claims 1-4 are cancelled herein. Claims 5-8 and 14-17 are amended herein. No claims are added herein. Support for the amendments to claims 5 and 14 can be found in the specification, for example, at page 9, lines 14-16. Amendments to claims 6-8 and 15-17 are made to correct typographical errors pointed out by the Examiner. Thus, claims 5-22 are pending.

B. The Claims are Enabled

The Action first rejects claims 1-22 under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Action acknowledges that the claims are enabled for a method of treating dry eye condition in a non-human mammal by administering to an eye of a non-human mammal a nucleic acid composition comprising a eukaryotic promoter operably linked to the nucleotide sequence disclosed in SEQ ID NO. 1 or 3 in an ocular drop, wherein the expression of the transgene resulting in treatment of dry eye condition. The Action asserts that the art of gene therapy is unpredictable and therefore the practice of the invention would require undue experimentation. Applicants respectfully traverse.

The corneal epithelia of many mammals contain significant activities of 15-LO. The inventors have shown that the ocular surface epithelium of postmenopausal women is lacking 15-LO. 15-LO is required for the synthesis of 15(S)-HETE, which in turn stimulates the production of MUC-1 mucin. The present invention provides methods for increasing the

expression of 15-LO-1 or 15-LO-2 in the ocular surface epithelium of postmenopausal women suffering from dry eye.

The cornea has been shown to be readily accessible to gene therapy by injection of naked plasma DNA into the cornea (Stechschulte *et al.*, *Invest. Ophthalm. Vis. Sci.* 42(9):1975-1979 (2001)). It has also been shown that exogenous nucleic acid may be introduced into ocular cells by contacting ocular cells with exogenous nucleic acid under conditions that allow the ocular cell to take up the exogenous nucleic acid into the ocular cell and express it. Such conditions are described, for example, in U.S. Patent no. 6,204,251 (Cuthbertson). In fact, Cuthbertson points out that "[g]ene therapy treatments are rapidly becoming a reality, with several dozen gene therapy protocols approved by the National Institutes of Health" (col. 1, lines 12-14). Cuthbertson describes general methods for effecting expression of an exogenous gene in ocular cells. Cuthbertson is incorporated by reference into the present specification.

The Federal Circuit reiterated the general standard for enablement in *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993). Essentially, the *Wright* court stated that an enabling specification teaches those skilled in the art how to make and use the claimed invention in its full scope without "undue experimentation." *Wright*, 999 F.2d at 1560. It is well settled patent law that the first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). This objective enablement may be provided through broad terminology or illustrative examples. *Id.* The PTO bears the initial burden, in rejecting a claim under the enablement requirement

of § 112, to set forth "a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *Wright*, 999 F.2d at 1561-62 (citing *Marzocchi*, 439 F.2d at 223-24, 169 USPQ at 369-70).

Section 112 requires that the patent specification describe the invention "in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...." 35 U.S.C. § 112. The enablement requirement is meant to ensure that the patent discloses sufficient information so that with the patent specification and knowledge in the art, a person with skill in the relevant field can make and use the claimed invention without undue experimentation. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1571 (Fed. Cir. 1991). It is submitted that the claims are enabled when read in light of the specification, including the art that is incorporated by reference into the specification. That is, the skilled artisan would reasonably expect the claimed invention to work as described.

In light of the foregoing arguments, Applicants respectfully request that the enablement rejection be withdrawn.

C. The Claims are Patentable Over Cuthbertson in view of Brash, Liminga, Yanni and Peterson

Next, the Action rejects claims 1-22 as being unpatentable over Cuthbertson, in view of Brash, Liminga, Yanni and Peterson. Cuthbertson is said to describe a method of treating ocular disease conditions using exogenous nucleic acid into ocular cells such that the protein

is expressed and the condition is treated. The Action acknowledges that Cuthbertson lacks a teaching of treatment of dry eye in postmenopausal women by expressing 15-lipoxygenase-1 or -2. Peterson is said to describe factors that cause dry eye conditions in postmenopausal women. The Action acknowledges that Peterson does not teach how dry eye conditions could be treated. Brash is said to describe the presence of 15-lipoxygenase mRNA in cornea. Liminga is said to disclose the presence of 15-lipoxygenase cDNA in cornea through metabolic studies, wherein it was established that human cornea synthesizes 15S-HETE from arachidonic acid. The Action acknowledges that neither Brash nor Liminga describe the role of 15-lipoxygenase-1 or -2 or 15-HETE in the treatment of dry eye. Yanni is said to disclose compositions of 15-HETE in therapeutic effective amount for the production of mucins and the administration of such compositions topically to treat dry eye. The Action acknowledges that Yanni does not teach the use of a transgene in a vector that could be expressed in a patient suffering from dry eye. The Action reasons that the skilled artisan would have been motivated to administer genes associated with arachidonic acid (AA) metabolites using appropriate vector for the treatment of dry eye condition because Peterson describe prevalence of dry eye conditions in postmenopausal women, Liminga teaches presence of 15-lipoxygenase in cornea which also synthesizes 15(S)-HETE and Yanni teaches compositions that include 15(S)-HETE for the mucins production that in turn increases tear production. Applicants respectfully traverse.

It is important to note that not one of the references cited in the Action discusses the nucleic acid sequence encoding 15-lipoxygenase-1 or -2 or its under-expression in post-

menopausal women. Cuthbertson discusses gene therapy methods for treatment of ocular disorders, but does not contain a teaching, or even a suggestion, of the administration of the nucleic acid sequence of 15-lipoxygenase-1 or -2 to treat dry eye in postmenopausal women. It is submitted that even if the skilled artisan were to combine Cuthbertson with the cited secondary references, he or she would not arrive at the claimed invention, which is the treatment of dry eye in a postmenopausal patient by incorporating a nucleic acid encoding the 15-lipoxygenase-1 or -2 protein into an ocular cell of the patient. This is because the present inventors were the first to demonstrate that the ocular surface epithelium of postmenopausal women is lacking 15-LO.

Determining obviousness requires an analysis of the invention *as a whole*. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). Significantly, *Gillette* emphasizes that whether all of the elements of the claimed invention were old in other contexts is immaterial to the issue of obviousness. Rather, "*what must be found obvious to defeat the patent is the claimed combination.*" *Id.* (quoting *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448, 223 U.S.P.Q. 603, 609-10 (Fed. Cir. 1984)) (emphasis in original).

It is well settled patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *See In re Fine*, 837 F.2d

1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); MPEP § 2143.01.

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. For example, the Federal Circuit held in *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990), that the mere fact that combination or modification of a reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *Mills*, 16 U.S.P.Q.2d at 1432; *see also* MPEP § 2143.01, page 2100-91.

Moreover, the Board of Patent Appeals and Interferences has held that the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish obviousness. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (BPAI 1993). Section 2143.01 of the MPEP explains the *Levengood* holding as follows:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.
>
> MPEP § 2143.01, page 2100-91 (emphasis in original).

The present invention provides methods for treating dry eye in a postmenopausal patient by incorporating a nucleic acid encoding the 15-lipoxygenase-1 or -2 protein into an ocular cell such that the nucleic acid is expressed. It is submitted that the Action has taken

the teaching of the present application that the ocular surface epithelium of postmenopausal women is lacking 15-LO and combined it with the disclosure in Cuthbertson that ocular disorders may be treated with gene therapy to state that it would have been obvious for one skilled in the art to treat dry eye in postmenopausal women by causing increased expression of 15-LO-1 or -2. This amounts to an improper "hindsight reconstruction" of the invention based upon the teaching in the present application. *See In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). In *Fine*, the court explained that

> [t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Fine, 5 U.S.P.Q.2d at 1600 (quoting *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983)).

The rejection under § 103 based on the combination of Cuthbertson, Brash, Liminga, Yanni and Peterson amounts to a "picking and choosing" of certain parts of the references while ignoring other aspects of it. In fact, there is nothing within Brash, Liminga, Yanni or Peterson that, when combined with Cuthbertson, would result in the presently claimed invention, since not one of the secondary references mentions the connection between decreased expression of 15-LO-1 or -2 and dry eye in postmenopausal women. In fact, only Peterson mentions postmenopausal women and dry eye in such patients and it only discusses such dry eye in relation to the occurrence of rosacea in such patients. Again, this is because it was the present inventors who first discovered the deficiency of 15-LO-1 or -2 expression in the eyes of

postmenopausal women. The Federal Circuit has held that "it is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference *fairly suggests* to one skilled in the art." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 416, 419 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (CCPA 1965)). What the Action ignores is the fact that nowhere within Cuthbertson, Brash, Liminga, Peterson and Yanni is a method for treating dry eye in postmenopausal women by causing increased expression of 15-LO-1 or -2 by incorporation of nucleic acid sequences encoding the same into the eye of such patients taught.

In light of the foregoing arguments, Applicants respectfully request that the obviousness rejection be withdrawn.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 551-4321 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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